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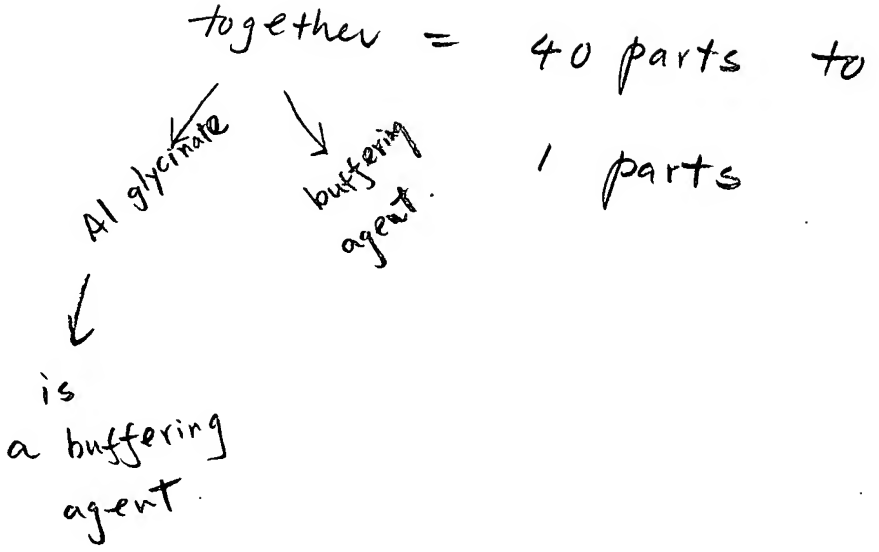
(54) STABILIZED ANTIULCER AGENT-CONTAINING PREPARATION

(57) Abstract:

PURPOSE: To stabilize a specific benzimidazole compound by adding aluminum glycinate and a buffering agent as stabilizers to the benzimidazole compound, the benzimidazole compound having an excellent gastric acid secretion-inhibiting activity and an excellent antiulcer activity, being low toxic and being unstable against acids.

CONSTITUTION: A 2-[(2-pyridyl) methylsulfinyl] benzimidazole compound having an excellent antiulcer activity and unstable against acids is compounded with aluminum glycinate and a buffering agent (preferably disodium hydrogenphosphate) as stabilizers for the stabilization of the compound. The aluminum glycinate and the buffering

agent are desirably compounded in amounts of 0.1-20 pts.wt. and 0.01-20 wt., respectively, per pt.wt. of the benzimidazole compound. The preparation is a little in the change of the appearance even when stored for a long period, does substantially not cause the lowering of the content of the ingredient and exhibits excellent stability. The preparation is especially effective for treating gastrointestinal ulcer, etc.



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(54) [Title of invention] Stabilized antiulcer agent-containing preparation

(57) [Abstract]

[Constitution] A stabilized antiulcer agent-containing preparation distinguished in that a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound, which has an antiulcer effect and is unstable in acid, is compounded with aluminum glycinate and a buffering agent as stabilizers.

[Benefit] It was discovered that when benzimidazole compounds unstable in acid are compounded and with a combination of aluminum glycinate and buffering agent, the benzimidazole compound is markedly stabilized, and coloration does not take place. Thus, the use of these stabilizers allows a stabilized antiulcer agent-containing preparation to be obtained.

[Claims]

[Claim 1] A stabilized antiulcer agent-containing preparation distinguished in that a 2–[(2–pyridyl)methylsulfinyl]benzimidazole compound, which has an antiulcer effect and is unstable in acid, is compounded with aluminum glycinate and a buffering agent as stabilizers.

[Detailed description of the invention]

[0001]

[Field of industrial application] The present invention relates to stabilized antiulcer agent-containing preparations.

[Prior art and problems to be solved by the invention] 2–[(2–pyridyl)methylsulfinyl] benzimidazole compounds having an H^+–K^+ ATPase inhibitory effect (hereinafter also referred to simply as benzimidazole compounds) are useful as peptic ulcer treatment agents that strongly suppress gastric acid secretion. Because their action is strong and sustained, they have received attention as next-generation peptic ulcer treatment agents to replace histamine H_2 receptor antagonists such as cimetidine. In particular, the gastric acid secretion suppressant effect of the benzimidazole compounds described in Unexamined Patent Publications SHO54-141783, SHO61-50978, HEI1-6270, etc., is strong, and their clinical utility has been confirmed. However, these benzimidazole compounds have poor stability, being unstable against temperature, humidity and light when in a solid state, and rapidly disintegrating and coloring when in an acidic to neutral aqueous solution. Furthermore, in pharmaceutical preparations such as tablets, pellets, granules, capsules and powders, they are affected by other ingredients in the formula, becoming unstable and undergoing chronological loss in content and discoloration. Moreover, among these preparations, when tablets or granules are provided with a coating, the compounding properties with enteric substrates (cellulose acetate phthalate, hydroxypropyl methyl cellulose, hydroxymethyl cellulose acetate succinate, methacrylic acid/acrylic acid copolymer, etc.) is poor, and loss in content and coloration occur. In this way, while production of oral preparations of benzimidazole compounds requires compounding with other ingredients and an enteric coating, because this has an adverse effect on stability as described above, creating such preparations was difficult. Thus, to make these compounds into preparations for oral administration, it is necessary to suitably stabilize them. Many stabilizers and stabilization methods have already been studied for obtaining a stable benzimidazole compound preparation having an antiulcer effect, such as the method of compounding with alkaline reactive compounds (Unexamined Patent Publication SHO62-258320), the method of compounding with magnesium or calcium basic inorganic salts (Unexamined Patent Publication SHO62-277322), the method of compounding with magnesium oxide and mannitol (Unexamined Patent Publication HEI2-22225), etc., but the development of

more useful stabilized preparations has been desired.

[0002]

[Means of solving the problems] The inventors, in view of this situation, as a result of concerted studies using various basic substances for the purpose of stabilizing benzimidazole compound-containing compositions, discovered that the aforementioned problem can be solved through the combined use of aluminum glycinate and buffering agent, thereby completing the present invention. That is, the present invention relates to a stabilized antiulcer agent-containing preparation distinguished in that a 2–[(2–pyridyl)methylsulfinyl]benzimidazole compound, which has an antiulcer effect and is unstable in acid, is compounded with aluminum glycinate and a buffering agent as stabilizers. In the present invention, the 2–[(2–pyridyl)methylsulfinyl] benzimidazole compound which has an antiulcer effect and is unstable in acid is specifically a compound as described in the aforementioned patent publications and the like, including for instance omeprazole (5-methoxy–2–[[(4–methoxy–3,5–dimethyl–2–pyridyl)methyl)sulfinyl]–1H–benzimidazole), lansoprazole (2–[[[3–methyl–4–(2,2,2–trifluoroethoxy)–2–pyridyl]methyl] sulfinyl]–1H–benzimidazole) or 2–[[4–(3–methoxypropoxy)–3–methyl–2–pyridyl]methylsulfinyl]–1H–benzimidazole sodium salt, etc.

[0003] The buffering agents used in the present invention include sodium tartrate, sodium acetate, sodium hydrogen carbonate, sodium carbonate, sodium polyphosphate, dipotassium hydrogen phosphate, sodium pyrophosphate, disodium hydrogen phosphate, trisodium phosphate and tripotassium phosphate; of these, disodium hydrogen phosphate is preferable. The compounding quantities in the present invention are desirably in the range of 0.1 to 20 parts by weight aluminum glycinate and 0.01 to 20 parts by weight buffering agent per 1 part by weight benzimidazole compound, but are not limited thereto. The inventive stabilizers may be added together with commonly used pharmaceutical additives, for instance excipients such as lactose, mannitol, corn starch and crystalline cellulose, binding agents such as hydroxypropyl cellulose, disintegrants such as low-substituted hydroxypropyl cellulose, carboxymethyl starch sodium (trade name: Explotab, Kimura Sangyo), carboxymethyl cellulose calcium and -starch, surfactants such as sodium lauryl sulfate and Tween 80 (trade name), lubricants such as magnesium stearate and talc, etc.

[0004] The inventive composition is obtained by mixing a benzimidazole compound, aluminum glycinate and a buffering agent, as well as the aforementioned additives and water as required, uniformly in a kneader. For the mixing method, the benzimidazole compound may be mixed with aluminum glycinate and buffering agent first and then mixed with additives, or one may mix the benzimidazole compound with additives and then add stabilizers thereto: any method may be

0.1 mg

0.11 mg

used so long as ultimately the stabilizers are in uniform contact with the benzimidazole compound. The obtained mixture is made into small granules by a wet granulation method, and are then tableted to obtained a base tablet for a tablet preparation. Alternately, one can make granules using an extrusion granulator and then prepare core granules for a granule preparation using a Marumerizer (made by Fuji Paudal).

[0005] The base tablets or core granules obtained in this manner can be covered with an enteric coating to make enteric preparations, but to avoid adverse effects from the enteric coating, the base tablet or core granules are covered with 1 to 2 layers of undercoating. Undercoating agents include hydroxypropyl methyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, etc.; the aforementioned aluminum glycinate, aluminum hydroxide, and if required, the aforementioned buffering agents may also be added to the undercoating layers. Moreover, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, hydroxymethyl cellulose acetate succinate, methacrylic acid/acrylic acid copolymer (trade name: Eudragit) and the like may be used for the enteric undercoating. In the above manner, it is possible to obtain enteric tablets or granules, which are suitable preparations for oral administration; moreover, the granules can be filled into capsules to make a capsule preparation. Preparations obtained in this manner exhibit excellent stability, undergoing little change in appearance and almost no loss in content even when stored for long periods. The inventive preparations have excellent gastric acid secretion suppressant effect and antiulcer effect, as well as having low toxicity, and thus can be used for treatment of peptic ulcers, etc., in mammals, including humans.

[0006]

[Embodiment examples] Below, the invention is explained in greater detail by presenting experiment examples and embodiment examples; the present invention is however not limited thereto.

Experiment example 1

100 mg omeprazole, aluminum glycinate and the buffering agent disodium hydrogen phosphate (Na_2HPO_4 $12H_2O$) were dispersed in 20 ml water and stored at 25°C to examine chronological change in appearance of the white suspension. Furthermore, chronological change in appearance at 25°C of control liquids not containing either the aluminum antacid or the buffering agent was observed.

[0007]

[Table 1]

Table 1

		Added substance	(mg)	Change in appearance at 25°C		
				1 day	3 days	7 days
Present invention		Aluminum glycinate	100	White	White	White
		Na_2HPO_4 $12H_2O$	30			
		Aluminum glycinate	100	White	White	White
		Na_2HPO_4 $12H_2O$	100			
Control		None	—	Light purple	Purple	Blackish purple
	Antacid	Aluminum glycinate	200	Faint purple	Brown	Brown
		Aluminum hydroxide	200	Purple	Purple	Purple
		Magnesium carbonate	200	White	Faint brown	Light brown
		Synthetic hydrotalcite	200	White	Faint gray	Light brown
	Buffering agent	Na_2HPO_4 $12H_2O$	200	Light brown	Light brown	Light brown
		Sodium tartrate	200	Light purple	Purple	Purple
		Sodium acetate	200	Faint brown	Light purple	Light purple
		Sodium hydrogen carbonate	200	White	Faint brown	Light purple
		Sodium polyphosphate	200	Faint brown	Faint brown	Light brown
		Dipotassium hydrogen phosphate	200	Light brown	Light brown	Light brown
		Sodium pyrophosphate	200	Faint brown	Faint brown	Light brown

[0008] The results were that coloration of omeprazole tended not to occur when aluminum glycinate and buffering agent were used in combination as compared to using either alone, showing that omeprazole was stabilized through the combined use.

[0009] Embodiment example 1

The following composition was placed in a kneader and mixed for approximately 20 minutes, after which a suitable quantity of water was added thereto and the mixture was kneaded and granulated in an extrusion granulator (screen diameter 1.0 mm), after which spherical granules were obtained with a Marumerizer (Fuji Paudal). These granules were dried for 30 minutes at a supply air temperature of 50°C in a fluidized dryer, and granules of 14 to 24 mesh were obtained using a sieve.

Omeprazole	5.0 mg
Aluminum glycinate	5.0 mg
Sodium pyrophosphate	2.0 mg
Crystalline cellulose	4.0 mg
Low-substituted hydroxypropyl cellulose	4.0 mg
Hydroxypropyl cellulose	0.5 mg

Mannitol	54.5 mg
Total	75.0 mg

[0010] Embodiment example 2

Granules were obtained from the following composition in a manner analogous to embodiment example 1. The disodium hydrogen phosphate (Na_2HPO_4 12 H_2O) was compounded after dissolving in purified water.

Omeprazole	5.0 mg
Aluminum glycinate	5.0 mg
Na_2HOP_4 $12H_2O$	1.5 mg
Crystalline cellulose	4.0 mg
Low-substituted hydroxypropyl cellulose	4.0 mg
Hydroxypropyl cellulose	0.5 mg
Mannitol	55.0 mg
Total	75.0 mg

[0011] Embodiment example 3

The granules obtained in embodiment example 2 were provided with coatings of the following composition to obtain enteric granules. Undercoatings 1 and 2 were applied in a fluidized spray dryer (Ogawara) at a supply air temperature of 75°C, exhaust temperature 55°C, and the enteric coating was applied at a supply air temperature of 65°C, exhaust temperature 50°C.

Granules from embodiment example 2	75.0 mg
Undercoating 1	
Hydroxypropyl methyl cellulose	3.5 mg
Aluminum glycinate	1.4 mg
Na_2HOP_4 $12H_2O$	0.1 mg
Talc	0.5 mg
Purified water	(64.5 mg)
Total	5.5 mg
Undercoating 2	
Hydroxypropyl methyl cellulose	3.5 mg
Titanium oxide	2.5 mg
Talc	0.5 mg
Purified water	(64.5 mg)
Total	6.5 mg

Enteric coating	
Hydroxypropyl methyl cellulose phthalate	10.7 mg
Cetanol	0.5 mg
Talc	1.8 mg
Methylene chloride	(33.0 mg)
Ethanol	(86.0 mg)
Purified water	(33.0 mg)
Total	13.0 mg

The obtained omeprazole enteric granules had excellent elution properties and were stable even when stored under heated and humidified conditions.

[0012] Embodiment example 4

Of the components indicated below, lansoprazole, aluminum glycinate, mannitol, starch, sodium lauryl sulfate and hydroxypropyl cellulose were mixed uniformly, sodium pyrophosphate dissolved in a suitable quantity of purified water was added thereto, kneading was carried out, and then the mixture was dried in a fluidizer dryer for 30 minutes at 50°C. The dried granulate was sorted with a 24 mesh sieve, magnesium stearate was added to it and mixed, and then tablets (base tablets) were produced at 135 mg per tablet using a rotary tablet machine.

Omeprazole	20.0 mg
Aluminum glycinate	20.0 mg
Sodium pyrophosphate	1.0 mg
Mannitol	71.7 mg
-starch	20.0 mg
Sodium lauryl sulfate	0.3 mg
Hydroxypropyl cellulose	1.0 mg
Magnesium stearate	1.0 mg
Total	135.0 mg

[0013] Embodiment example 5

The tablets (base tablets) obtained in embodiment example 4 were provided with coatings of the following composition to obtain enteric tablets. For undercoatings 1 and 2, coating was carried out using a Hi-Coater (Freund Industrial) at a supply air temperature of 70°C, exhaust temperature 40°C, pan speed 13 rpm. For the enteric coating, coating was carried out at a supply air temperature of 55°C, exhaust air temperature 37°C.

Tablets from embodiment example 4	135.0 mg
Undercoating 1	

Hydroxypropyl methyl cellulose	1.5 mg
Aluminum glycinate	0.35 mg
Na_2HOP_4 $12H_2O$	0.05 mg
Purified water	(23.0 mg)
Total	1.9 mg
Undercoating 2	
Hydroxypropyl methyl cellulose	3.1 mg
Titanium oxide	1.0 mg
Purified water	(56.0 mg)
Total	4.1 mg
Enteric coating	
Hydroxypropyl methyl cellulose phthalate	3.1 mg
Cetanol	0.2 mg
Talc	0.2 mg
Ethanol	(35.0 mg)
Purified water	(10.0 mg)
Total	3.5 mg
Grand total	144.5 mg

[0014] Embodiment example 6

Core granules of the following formula were produced in accordance with embodiment example 1. The sodium pyrophosphate used as stabilizer was compounded after diluting in purified water. Aluminum glycinate and Na_2HPO_4 $12H_2O$ were compounded into undercoating 1 in order to prevent compounding change between the enteric film and the omeprazole in the core granules. The film coatings were applied using a fluidized spray dryer (Ogawara). Undercoatings 1 and 2 were applied at a supply air temperature of 75°C, exhaust temperature 55°C, and the enteric coating was applied at a supply air temperature of 55°C, exhaust temperature 40°C.

Core granules	
Omeprazole	5.0 mg
Aluminum glycinate	10.0 mg
Sodium pyrophosphate	2.0 mg
Crystalline cellulose	4.0 mg
Low-substituted hydroxypropyl cellulose	4.0 mg
Hydroxypropyl cellulose	0.5 mg
Mannitol	44.5 mg

Total	70.0 mg
Undercoating 1	
Hydroxypropyl methyl cellulose	3.2 mg
Aluminum glycinate	1.2 mg
Na_2HOP_4 $12H_2O$	0.1 mg
Talc	0.5 mg
Purified water	(60.0 mg)
Total	5.0 mg
Undercoating 2	
Hydroxypropyl methyl cellulose	3.5 mg
Titanium oxide	1.0 mg
Talc	0.5 mg
Purified water	(65.0 mg)
Total	5.0 mg
Enteric coating	
Eudragit L-30D-55 (solid content)	15.0 mg
Polyethylene glycol 6000	1.3 mg
Tween 80	0.7 mg
Talc	3.0 mg
Purified water	(50.0 mg)
Total	20.0 mg
Grand total	100.0 mg

[0015] Reference example 1

Tablets (base tablets) were prepared using the following formula in accordance with embodiment example 4.

Omeprazole	20.0 mg
Mannitol	93.2 mg
-starch	20.0 mg
Sodium lauryl sulfate	0.3 mg
Hydroxypropyl cellulose	1.0 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

The obtained tablets (base tablets) were provided with the undercoating 2 and enteric coating from embodiment example 5 to obtain enteric tablets.

[0016] Reference example 2

Tablets (base tablets) were prepared using the following formula in accordance with embodiment example 4.

Omeprazole	20.0 mg
Aluminum glycinate	20.0 mg
Mannitol	73.2 mg
-starch	21.0 mg
Sodium lauryl sulfate	0.3 mg
Hydroxypropyl cellulose	1.0 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

The obtained tablets (base tablets) were provided with the film coating of embodiment example 5 to obtain enteric tablets.

[0017] Experiment example 2

The base tablets obtained in embodiment example 4, the enteric tablets obtained in embodiment example 5, the base tablets and enteric tablets obtained in reference example 1 and the base tablets and enteric tablets obtained in reference example 2 were placed into glass bottles, sealed under conditions of 60°C or left open under conditions of 40°C, 75% RH, and in each case left for two weeks. The results of change in appearance are indicated in Table 2.

[0018]

[Table 2]

Table 2

		At time of preparation	60°C sealed	40°C, 75% RH open
Embodiment example 4	(tablets)	White	White	White
Embodiment example 5	(enteric tablets)	White	White	White
Reference example 1	(base tablets)	Faint brown	Light brown	Light brown
	(enteric tablets)	White	Faint brown	Light brown
Reference example 2	(base tablets)	Light brown	Light brown	Light brown
	(enteric tablets)	Faint brown	Light brown	Light brown

[0019] As is clear from the results shown in Table 2, by compounding aluminum glycinate and buffering agent, change in appearance was markedly improved.

[0020]

[Benefits of the invention] When aluminum glycinate or buffering agent were each used alone

and compounded with a benzimidazole compound, as is clear from the experimental results, no stabilization effect was obtained, while when they were used together, it was found that the benzimidazole compounds were markedly stabilized. Thus, the combined use of aluminum glycinate and buffering agent allows a stabilized antiulcer agent-containing preparation to be obtained.